```
      (FILE 'USPAT' ENTERED AT 18:40:31 ON 17 SEP 1999)
L1         30427 S ANTIBODY
L2         11764 S L1(P)(CONJUGATE# OR CHIMER?)
L3           202 S L2(P)(CYTOKINE# OR CHEMOKINE# OR LYMPHOKINE#)
L4             3 S L3(P)(HER2 OR NEU)
L5             4 S L3(P)RANTES
L6             0 S L3(P)DC-CK1
L7             0 S L3(P)FRACTALKINE
L8             0 S L3(P)LYMPHTACTIN
L9             0 S L3(P)LYMPHOTACTIN
L10            0 S L3(P)MIG
L11            0 S L3(P)MCAF
L12            2 S L3(P)MIF
L13            0 S L3(P)NAP
L14         2209 S L1(P)CHIMER?
L15          456 S L14(P)(CANCER OR NEOPLAS? OR TUMOR# OR TUMOUR# OR MALIGN
AN?
L16            6 S L15(P)(HER2 OR NEU)
L17            0 S L15(P)RANTES
L18            2 S L14(P)(CHEMOKINE)
L19            0 S L14(P)RANTES
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Set	Items	Description
S1	6570	ANTIBODY(5N)(CHIMER?)
S2	4	S1(5N)(HER2 OR NEU)
S3	4	RD (unique items)
S4	4	S1(5N)(CHEMOKINE?)
S5	4	RD (unique items)
S6	34	L1(5N)CYTOKINE?
S7	14	RD (unique items)
S8	28	S1(5N)CYTOKINE?
S9	16	RD (unique items)
S10	20	S1(5N)LYMPHOKINE?
S11	11	RD (unique items)
S12	0	S1(5N)DC-CK1
S13	0	S1(5N)SDF-1
S14	0	S1(5N)FRACTALKINE
S15	0	S1(5N)LYMPHOTACTIN
S16	0	S1(5N)(IP-10 OR MIG OR MCAF OR MIP-12 OR MIP1.BETA OR IL-8 OR NAP-2 OR PF-4)
S17	0	S1(5N)RANTES
S18	1	DC-CK1
S19	29	SDF-1
S20	29	RD (unique items)
S21	0	S20(5N)(CANCER OR NEOPLAS? OR TUMOR? OR TUMOUR? OR MALIGNAN? OR METAST?)
S22	129	FRACTALKINE
S23	0	S22(5N)(CANCER OR NEOPLAS? OR TUMOR? OR TUMOUR? OR MALIGNAN? OR METAST?)
S24	74	RD S22 (unique items)
S25	352	LYMPHOTACTIN
S26	11	S25(5N)(CANCER OR TUMOR? OR TUMOUR? OR MALIGNAN? OR MATAST?)
S27	5	RD (unique items)
S28	155	IP-10
S29	0	S28(5N)(CANCER OR NEOPLAS? OR TUMOR? OR TUMOUR? OR MALIGNAN? OR MATAST?)
S30	145	RD S28 (unique items)
S31	3153	MIG
S32	38	S31(5N)(CANCER OR NEOPLAS? OR TUMOR? OR TUMOUR? OR MALIGNAN? OR METAST?)
S33	16	RD (unique items)
S34	647	MCAF
S35	52	S34(5N)(CANCER OR NEOPLAS? OR TUMOR? OR TUMOUR? OR MALIGNAN? OR METAST?)
S36	20	RD (unique items)
S37	0	MIP-1.ALPHA
S38	20	MIP-1
S39	20	RD (unique items)
S40	6	NAP-2
S41	6	RD (unique items)
S42	28	PF-4
S43	28	RD (unique items)
S44	0	S1(5N)RANTES
S45	5783	RANTES
S46	393	S45(5N)(CANCER OR NEOPLAS? OR TUMOUR? OR TUMOR? OR MALIGNAN? OR METAST?)
S47	183	RD (unique items)
S48	107	S47/1990:1997
S49	30634	ANTIBODY(5N)(CONJUGATE? OR FUSION)

S50	164	S49(5[redacted]CHEMOKINE? OR CYTOKINE? OR LYM[redacted]KINE? OR RANTES)
S51	87	RD ([redacted]ue items)
S52	7	AU="[redacted]ENBLATT, JOSEPH D."
S53	7	RD (unique items)
S54	14	AU="CHALLITA-EID PIA M":AU="CHALLITA, P.M."
S55	9	RD (unique items)
S56	27	AU="ABBOUD, C.N."
S57	27	RD (unique items)

US PAT NO: 5,942,602 [IMAGE AVAILABLE] L5: 1 of 4

SUMMARY:

BSUM(9)

It . . . aspect of the invention to provide a test kit comprising an EGF receptor and/or EGF receptor variants specific single chain **antibody** as mentioned above, e.g., **conjugated** or joined to a biologically-active component such as ETA, or **conjugated** to a MRI contrast agent, a radiodiagnostic agent, or a radiotherapeutic agent. By biologically active, it is meant that the. . . either on an in vitro or in vivo system. Biologically-active components includes, e.g., cytotoxins such as ETA or diphteria toxin, **cytokines** such as interferons (.alpha.-, .beta.- and .gamma.), interleukins, TNF-.alpha., **Rantes**, MIP, hormones, estrogens, growth factors, etc. See, e.g., Siegall et al., Drug Development Research, 34:210-219, 1995 for other cytotoxins or immunotoxins. The biologically-active component can be covalently joined to the **antibody**, or noncovalently joined, e.g., by hydrogen or ionic bonds. If the biologically-active component is a peptide, it can be fused. . . ion. A single chain polypeptide in accordance with the present invention also includes polypeptides which have the characteristics of monoclonal **antibody** 14E1. By the phrase "has the characteristics of," it is meant that the polypeptide binds to the same epitope or. . . 14E1. The polypeptide can also have substantially the same binding affinity and/or tissue specificity and/or a

PAT NO: 5,821,337 [IMAGE AVAILABLE] L16: 1 of 6

DETDESC:

DETD(4)

The murine monoclonal **antibody** known as muMAb4D5 (Fendly, B. M. et al., **Cancer** Res. 50: 1550-1558 (1990)) is directed against the extracellular domain (ECD) of p185.sup.**HER2**. The muMAb4D5 and its uses are described in PCT application WO 89/06692 published 27 Jul. 1989. This murine **antibody** was deposited with the ATCC and designated ATCC CRL 10463. In this description and claims, the terms muMAb4D5, chMAb4D5 and huMAb4D5 represent murine, **chimerized** and humanized versions of the monoclonal **antibody** 4D5, respectively.

US PAT NO: 5,712,149 [IMAGE AVAILABLE] L16: 3 of 6

DETDESC:

DETD(27)

Various . . . as CD4, CD8, cytokine or hormone receptors or adhesion molecules. The receptor may be responsive to a natural ligand, an **antibody** or fragment thereof, a synthetic molecule, e.g., drug, or any other agent which is capable of inducing a signal. Thus, in addition to CD receptors, ligands for receptors expressed on **cancer** cells could supply the extracellular domain of the **chimeric** receptors of the invention. For example human Heregulin (Hrg) a protein similar in structure to Epidermal Growth Factor (EGF), has. . . surface of breast carcinoma cells and ovarian carcinoma calls (Holmes et al., Science 256:1205-1210 (1992)). The murine equivalent is the "**Neu**" protein (Bargman et al., Nature 319:226-230 (1986)). The extracellular domain of Hrg could be joined to the CD28 or CD4 transmembrane domain and the CD28 co-stimulatory receptor cytoplasmic domain to form a **chimeric** construct of the invention to augment the effector function of T cells to kill breast carcinoma cells. In addition, either member of a ligand/receptor pair, where one is expressed on a target cell such as **cancer** cell, a virally infected cell or an autoimmune disease cause cell may be used as an extracellular domain in the. . .

US PAT NO: 5,888,809 [IMAGE AVAILABLE] L18: 2 of 2

SUMMARY:

BSUM(11)

The invention further provides **chimeric** recombinant DNA molecules wherein the CHEF1 DNA is operably linked to (i.e., promotes transcription of) gene sequences encoding a desired protein product. **Chimeric** molecules in general are those comprising domains not normally found in association in a wild-type environnment; in the present invention, a **chimeric** DNA can comprise part or all of the CHEF1 regulatory DNA in association with a DNA sequence other than the gene encoding hamster EF-1.alpha. protein. Protein products encoded by the **chimeric** molecules include physiologically active proteins, portions or subunits of active proteins, as well as marker, or reporter, proteins. The polynucleotide. . . an exogenous source being one other than the genome of a CHO cell, including, for example, a synthesized DNA. Preferred **chimeric** molecules of the invention include those wherein CHEF1 DNA is operatively linked to DNA encoding: (i) the heavy chain of anti-ICAM3 **antibody** ICM3, (ii) the light chain of ICM3, (iii) the heavy chain of anti-CD11/CD18 **antibody** hu23F2G, (iv) the light chain of hu23F2G, (v) chitinase, (vi) platelet activating factor acetyl hydrolase (PAF-AH), and (vii) macrophage derived **chemokine** (MDC). Bacterial host cells transformed with plasmid DNA comprising the

51/7/59 (Item 11 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02670448

Utility

RECOMBINANT **ANTIBODY CYTOKINE FUSION** PROTEINS
[RECOMBINANT IMMUNOGLOBULIN CHAIN]

PATENT NO.: 5,650,150
ISSUED: July 22, 1997 (19970722)
INVENTOR(s): Gillies, Stephen D., 245 Leavitt St., Hingham, MA (Massachusettes), US (United States of America), 02043 [Assignee Code(s): 68000]
EXTRA INFO: Assignment transaction [Reassigned], recorded October 27, 1995 (19951027)

POST-ISSUANCE ASSIGNMENTS

ASSIGNEE(s): GILLIES, STEPHEN D. 159 SUNSET ROAD CARLISLE, MASSACHUSETTS 01741
Assignor(s): SMITH, SANDFORD D., PRESIDENT AND CEO -- signed: 10/12/1995
Recorded: October 27, 1995 (19951027)
Reel/Frame: 7711/0848
Brief: ASSIGNMENT OF ASSIGNOR'S INTEREST
Rep.: TESTA, HURWITZ & THIBEAULT GILLIAN M. FENTON HIGH STREET TOWER 125 HIGH STREET BOSTON, MA 02110

APPL. NO.: 8-281,238
FILED: July 27, 1994 (19940727)

This is a continuation of application Ser. No. 07-788,765 filed Nov. 7, 1991 (now abandoned), which is a continuation-in-part of application Ser. No. 07-612,099, filed Nov. 9, 1990 (now abandoned), the disclosures of which are incorporated herein by reference.

FULL TEXT: 699 lines

ABSTRACT

Immunoconjugates for the selective delivery of a cytokine to a target cell are disclosed. The fusion proteins are comprised of an immunoglobulin heavy chain having a specificity for the target cell, such as a cancer or virus-infected cell, and a cytokine, such as lymphotoxin, tumor necrosis factor alpha, interleukin-2, or granulocyte-macrophage colony stimulating factor, joined via its amino terminal amino acid to the carboxy-terminus of the immunoglobulin. Nucleic acid sequences encoding these fusion proteins and methods of their preparation by genetic engineering techniques are also disclosed.

02665588
Utility

THERAPEUTIC ANTIBODY BASED FUSION PROTEINS
[Antitumor]

PATENT NO.: 5,645,835
ISSUED: July 08, 1997 (19970708)
INVENTOR(s): Fell, Jr. Henry Perry, Redmond, WA (Washington), US (United States of America)
Gayle, Margit Ann, Woodinville, WA (Washington), US (United States of America)
ASSIGNEE(s): Oncogen, (A U.S. Company or Corporation), Seattle, WA (Washington), US (United States of America)
[Assignee Code(s): 14317]
APPL. NO.: 8-247,437
FILED: May 23, 1994 (19940523)

The present application is a division of prior U.S. application Ser. No. 07-468,390, filed on Jan. 22, 1990, now U.S. Pat. No. 5,314,995.

FULL TEXT: 645 lines

ABSTRACT

The present invention relates to methods of providing a targeted, amplified antitumor immune response using antibody-based fusion proteins. More specifically, the invention relates to the use of antibody-based fusion proteins comprising an immunoglobulin portion capable of binding to a tumor antigen linked to a biologically active lymphokine. The immunoglobulin portion targets the fusion protein to the site of the tumor cells and the lymphokine portion stimulates the proliferation of immune T cells at the site of the tumor cells, thereby amplifying the anti-tumor immune response. In preferred embodiments of the invention, the immunoglobulin portion of the fusion protein is derived from the L6 monoclonal antibody and/or the lymphokine is interleukin-2.

What is claimed is:

1. A method of increasing an antitumor immune response comprising exposing tumor cells, in the presence of immune effector cells, to an antibody-based fusion protein comprising a variable region of an immunoglobulin molecule capable of binding to an antigen on the surface of the tumor cell linked via peptide linkage to an IL-2 molecule capable of promoting lymphocyte proliferation.

2. The method of claim 1 in which the variable region of the antibody-based fusion protein is derived from the L6 antibody, produced by hybridoma L6 deposited with the ATCC and having accession number HB 8677.

9/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07730674 BIOSIS NO.: 000092055305
TARGETING OF TUMOR NECROSIS FACTOR TO TUMOR CELLS SECRETION BY MYELOMA CELLS OF A GENETICALLY ENGINEERED ANTIBODY-TUMOR NECROSIS FACTOR HYBRID MOLECULE

AUTHOR: HOOGENBOOM H R; RAUS J C M; VOLCKAERT G
AUTHOR ADDRESS: DR. L. WILLEMS-INSTITUUT, UNIVERSITAIRE CAMPUS, B-3610 DIEPENBEEK, BELG.

JOURNAL: BIOCHIM BIOPHYS ACTA 1096 (4). 1991. 345-354.
FULL JOURNAL NAME: Biochimica et Biophysica Acta
CODEN: BBACA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The construction, synthesis and secretion of a genetically engineered antibody-cytokine fusion molecule is described. To target tumor necrosis factor (TNF) to tumor cells, recombinant antibody technique were used to produce a Fab-like antibody-TNF conjugate. At the gene level, the heavy chain gene of an antitransferrin receptor antibody was linked to a synthetic TNF gene encoding human TNF. Transfection of the heavy chain-TNF gene into a myeloma derived cell line which was producing the light chain of the same antibody, allowed the isolation of a cell line secreting a fusion protein of the expected molecular weight and composition. The culture supernatant of the cell line contained TNF cytotoxic activity towards murine L929 cells and human MCF-7 cells. Cytotoxicity towards the human cancer cells was inhibited by an excess of the original antitransferrin receptor antibody, indicating that the antibody-TNF molecules are targeted to the transferrin receptor rich tumor cells. Since the antibody genes used are chimeric (i.e. composed of mouse variable and human constant regions) and since DNA encoding human TNF was used, the hybrid protein is an example of a humanized immunotoxin-like molecule. These results illustrate the possibilities of antibody engineering technology to create and produce improved agents for cancer therapy. Furthermore, they demonstrate for the first time the ability of myeloma cells to secrete an **antibody-cytokine chimeric** molecule.

A

20/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12029011 BIOSIS NO.: 199900309530
Modulation of CXCR4 expression and SDF-1 functional activity during differentiation of human monocytes and macrophages.

AUTHOR: Gupta S K(a); Pillarisetti K(a); Lysko P G(a)
AUTHOR ADDRESS: (a)Department of Cardiovascular Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 1, USA

JOURNAL: FASEB Journal 13 (7):pA1504 April 23, 1999

CONFERENCE/MEETING: Annual Meeting of the American Societies for Experimental Biology on Biochemistry and Molecular Biology 99 San Francisco, California, USA May 16-20, 1999
SPONSOR: American Societies for Experimental Biology

ISSN: 0892-6638
RECORD TYPE: Citation

20/3/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11533081 BIOSIS NO.: 199800314413
Differential chemotactic behavior of developing T cells in response to thymic chemokines.

AUTHOR: Kim Chang H; Pelus Louis M; White John R; Broxmeyer Hal E(a)
AUTHOR ADDRESS: (a)Dep. Microbiol./Immunol., Indiana Univ. Sch. Med., Build. R4, Room 302, 1044 W. Walnut St., Indi, USA

JOURNAL: Blood 91 (12):p4434-4443 June 15, 1998
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

20/3/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11510805 BIOSIS NO.: 199800292137
MCP-1 and MIP-1, but not RANTES, SDF-1 or IP-10 induce the migration of human T cells into human skin sites and their action depends on the presence of human endothelium.

AUTHOR: Kunstfeld Rainer; Lechleitner Sonja; Wolff Klaus; Petzelbauer Peter
AUTHOR ADDRESS: Dep. Dermatol., Univ. Vienna Med. Sch., Vienna, Austria

JOURNAL: Journal of Dermatological Science 16 (SUPPL. 1):pS30 March, 1998

CONFERENCE/MEETING: Third Joint Meeting of the European Society for Dermatological Research, Japanese Society for Investigative Dermatology, Society for Investigative Dermatology Cologne, Germany May 7-10, 1998
SPONSOR: European Society for Dermatological Research

ISSN: 0923-1811
RECORD TYPE: Citation
LANGUAGE: English

20/3/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11490923 BIOSIS NO.: 199800272255
Mature dendritic cells respond to SDF-1, but not to several beta-chemokines.

AUTHOR: Delgado Elena(a); Finkel Victoria; Baggiolini Marco; Mackay Charles R; Steinman Ralph M; Granelli-Piperno Angela
AUTHOR ADDRESS: (a)Lab. Cell. Physiol. Immunol., Rockefeller Univ., 1230 York Ave., New York, NY 10021, USA

JOURNAL: Immunobiology 198 (5):p490-500 March, 1998
ISSN: 0171-2985

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

30/7/70 (Item 70 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10910652 BIOSIS NO.: 199799531797
Antibodies to IP-10 and MIG block IL-12 mediated T-cell infiltration and RENCA tumor regression.

AUTHOR: Tannenbaum C; Tubbs R; Finke J; Bukowsi R; Hamilton T
AUTHOR ADDRESS: Cleveland Clinic Foundation, Cleveland, OH 44195, USA

JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 38 (0):p357-358 1997

CONFERENCE/MEETING: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X
RECORD TYPE: Citation

36/7/6 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09353097 BIOSIS NO.: 199497361467
Induction and regulation of IL-8 and **MCAF** production in human brain **tumor** cell lines and brain tumor tissues..

AUTHOR: Morita Mitsuya; Kasahara Tadashi; Mukaida Naofumi; Matsushima Kouji ; Nagashima Tadashi; Nishizawa Masatoyo; Yoshida Mitsuo
AUTHOR ADDRESS: Dep. Med. Biol. Parasitol., Jichi Med. Sch., Minamikawachi-machi, Tochigi-ken, 329-04, Japan

JOURNAL: European Cytokine Network 4 (5):p351-358 1993
ISSN: 1148-5493
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In order to elucidate the role of inflammatory cytokines in the central nervous system, we examined the production of two leukocyte chemoattractants, IL-8 and monocyte chemotactic and activating factor (**MCAF**) in brain **tumor** cell lines. The glioma cell lines tested exhibited high levels of IL-8 and MCAF mRNA expression upon stimulation with IL-1 or TNF-alpha, while none of the neuroblastoma cell lines expressed these cytokine mRNA. Both IL-8 and MCAF mRNA expression depended on the dose of IL-1-alpha and TNF-alpha and appeared very rapidly, reaching maximal levels at 3-6 hr, with substantial production of these cytokines in the culture supernatants. When various immunosuppressive drugs were tested, glucocorticoids but not other immunosuppressive drugs markedly inhibited the IL-1 or TNF-alpha-induced IL-8 and MCAF mRNA accumulation, suggesting that glucocorticoid is a potent regulator of these inflammatory cytokine production in the neural tissues. In addition, reverse transcription-polymerase chain reaction (RT-PCR) revealed the expression of IL-8 and **MCAF** mRNA expression in resected brain **tumor** tissues including glioblastoma, astrocytoma grade 2, ependymoma and medulloblastoma, indicating that these inflammatory cytokines are expressed in vivo.

36/7/7 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08999020 BIOSIS NO.: 199497007390
Synergism between human recombinant monocyte chemotactic and activating factor and lipopolysaccharide for activation of antitumor properties in human blood monocytes.

AUTHOR: Singh Rakesh K; Fidler Isaiah J(a)
AUTHOR ADDRESS: (a)Dep. Cell Biol., Box 173, Univ. Texas M. D. Anderson Cancer Cent., 1515 Holcombe Boulevard, Hous, USA

JOURNAL: Lymphokine and Cytokine Research 12 (5):p285-291 1993
ISSN: 1056-5477
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Monocyte chemotactic and activating factor (MCAF) is an important mediator of monocyte recruitment to sites of chronic inflammation and neoplasia. In the present study, we determined whether MCAF can also enhance the activation of tumoricidal capacity of monocytes. Human monocytes incubated that MCAF and subthreshold concentrations of lipopolysaccharide (LPS) exhibited synergistic tumoricidal activity against allogeneic A375 melanoma cells, irrespective of their **metastatic** potential. The sequence of **MCAF** and LPS treatment was crucial. Monocytes treated first with MCAF for 4 h and then with LPS for 18 h were highly cytotoxic to the melanoma cells, whereas monocytes first treated with LPS and then with MCAF were not. Treatment of monocytes with MCAF and LPS also significantly increased production of tumor necrosis factor. These data suggest that like interferon-gamma, MCAF can prime human monocytes to respond to LPS. Interleukin-8, a chemokine for neutrophils, did not enhance the monocytes' LPS-triggered tumoricidal response. Collectively, these data show that **MCAF** can influence the recruitment and **tumoricidal** activation of blood monocytes. Therefore, **MCAF** may be an important mediator of tumor regression.

51/7/2 (Item 2 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01700625 SUPPLIER NUMBER: 19563048 (THIS IS THE FULL TEXT)
Antibody fusion proteins used as potential treatment for B-cell malignancies.
Cancer Weekly Plus, n9, p19(2)
June 30,
1997

TEXT:

Two fusion proteins for the treatment of B-cell malignancies offer potential tumor-killing effects and tumor-targeting properties.

B-cell malignancies are cancers of the blood, lymph nodes, and bone marrow.

The pre-clinical study findings were published in the June 15, 1997, issue of Blood by Techniclone Corp., Tustin, California, scientists and researchers at the University of Southern California (USC). Techniclone holds patented rights to the antibodies from which these conjugates are generated.

The fusion proteins in this study were generated from a monoclonal antibody linked to a cytokine (a polypeptide that helps to stimulate anti-tumor immune responses) such as interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Mice with human B-cell tumors were injected with the fusion proteins, and were then evaluated at one, three, and five days after the injection.

In vitro cell toxicity studies showed approximately a 10-fold increase in tumor-killing effect of both tested fusion proteins over the monoclonal antibody alone, while internal distribution and imaging studies indicated that the fusion proteins specifically targeted the tumors. These data suggest that the fusion proteins have potential as a new treatment for B-cell cancers, such as multiple myeloma, lymphomas, and leukemias.

"We continue to be excited about the latest proprietary technologies emerging from our laboratories," said Alan Epstein, M.D., Ph.D., University of Southern California Medical Center and Techniclone. "We believe our research in fusion proteins may result in significant expansion of indications for cancer to potentially include the treatment of a variety of solid tumors."

"These encouraging findings provide another step toward the further develop- ment of our product pipeline of less toxic, more humane cancer therapies," said Lon H. Stone, Techniclone. "We consider this promising **antibody-cytokine fusion** protein to be a complementary adjunct to our most advanced drug development program, LYM-1, a non-Hodgkin's B-cell lymphoma therapy, in a mul- ti-stage treatment plan for this devastating disease."

51/7/23 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10628136 BIOSIS NO.: 199699249281
Targeting gamma interferon to tumor cells by a genetically engineered fusion protein secreted from myeloma cells.

AUTHOR: Xiang Jim(a); Qi Yumin; Cook Dan; Moyana Terence
AUTHOR ADDRESS: (a)Saskatoon Cancer Cent., 20 Campus Drive, Saskatoon, SK S7N 4H4, Canada

JOURNAL: Human Antibodies and Hybridomas 7 (1):p2-10 1996
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The construction, synthesis and expression of a genetically engineered bifunctional **antibody/cytokine fusion** protein is described To target IFN-tau to tumor cells, recombinant antibody techniques were used to construct a RM4/IFN-tau fusion protein containing the chimeric anti-tumor F(ab')-2 (RM4) and the IFN-tau moiety. The recombinant cDNA of IFN-tau was linked to 3 prime end of the chimeric heavy-chain gene fragment (M4) containing the V-H, the C-H1 and the hinge region to form the fused heavy-chain gene fragment M4-IFN-tau. Transfection of the M4-IFN-tau gene fragment into a myeloma derived cell line V-KC-K which produced the chimeric light-chain of the same antibody, allowed the transfectant secreting the bifunctional fusion protein RM4/IFN-tau. The RM4/IFN-tau was purified by the affinity chromatography. Our data showed that the PM4/IFN-tau retained the TAG72 antigen-binding reactivity as well as the IFN-tau activity as measured in ELISA, FACS analysis of cell-surface TAG72 expression, immunohistochemical study, and up-regulation of cell-surface expression of CEA, HL4 class I and class II antigens. Therefore, the bifunctional fusion protein RM4/IFN-tau may prove to be useful in targeting biological effects of the IFN-tau to tumor cells and in this way to stimulate the immune destruction of tumor cells.

51/7/28 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09983463 BIOSIS NO.: 199598438381
Recombinant **antibody-cytokine fusion** proteins for cancer immunotherapy.

AUTHOR: Reisfeld R A; Becker J C; Pancock J D
AUTHOR ADDRESS: Scripps Res. Inst., La Jolla, CA, USA

JOURNAL: Experimental Hematology (Charlottesville) 23 (8):p794 1995

CONFERENCE/MEETING: 24th Annual Meeting of the International Society for Experimental Hematology Duesseldorf, Germany August 27-31, 1995
ISSN: 0301-472X
RECORD TYPE: Citation

51/7/30 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08902309 BIOSIS NO.: 199396053810
Biological activity and in vivo clearance of antitumor **antibody-cytokine fusion** proteins.

AUTHOR: Gillies Stephen D(a); Young Delano; Lo Kin-Ming; Roberts Stanley
AUTHOR ADDRESS: (a)Fuji ImmunoPharmaceuticals Corp., 125 Hartwell Ave., Lexington, MA 02173, USA

JOURNAL: Bioconjugate Chemistry 4 (3):p230-235 1993
ISSN: 1043-1802
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Several human cytokines including IL-2, GM-CSF, and tumor necrosis factor alpha and beta were engineered as fusion proteins to the carboxyl terminus of a chimeric anti-ganglioside antibody, ch14.18, and expressed in transfected hybridoma cells. All of the fusion proteins were expressed at high levels and were easily purified by affinity or ion-exchange chromatography from culture supernatants. The effect of fusion of antigen binding activity was tested and found to vary with particular cytokine. No significant decreases in antigen binding were observed, and fusion of IL-2 had the greatest positive effect in a direct antigen binding assay. All fusion proteins maintained normal levels of biological activity except for GM-CSF, which was approximately 20% active, compared to recombinant GM-CSF produced in bacteria. The clearance of the fusion proteins was examined in normal Balb/c mice after intraperitoneal injection or in athymic (nu/nu) mice after intravenous injection and was generally quite rapid, relative to ch14.18. This was mainly due to a very rapid initial clearance rate (alpha phase) since the half-lives of the beta phase of the fusion proteins (about 30 h) were comparable to that of the free antibody (about 58 h). These results demonstrate that biologically active **antibody/cytokine fusion** proteins can be constructed by genetic engineering. Their relatively rapid clearance may require constant infusion rather than bolus injection in order to achieve clinical efficacy.

[formyl-methionyl-l[redacted]yl-phenylalanine]) and of appr[redacted]iate monoclonal anytibodies may pe[redacted] manipulation of the inflamma[redacted] response to human tumors. fMLP was c[redacted]ugated with 2 monoclonal antib[redacted]es (OC125 and OC133) which react with human ovarian carcinomas. Conjugates retained the ability to bind to a human ovarian carcinoma line (OVCA433) judged by indirect immunofluorescence and by radioimmunoassay. The fMLP conjugate was maximally chemotactic for human blood monocytes and human peritoneal macrophages at protein concentrations of 300-900 .mu.g/ml. Conjugates stimulated chemotaxis rather than **chemokinesis**. After incubation with an fMLP-**antibody conjugate**, antigen positive OVCA433 cells released chemotactic activity and attracted monocytes in vitro; an antigen-negative ovarian cell line failed to do so. As monocytes can be important effectors of antibody dependent cell mediated cytotoxicity, fMLP conjugates might increase monocyte concentrations at tumor sties and potentiate serotherapy for certain human neoplasms.

51/7/37 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07628694 EMBASE No: 1999063406
Immune directed therapy for ovarian carcinoma
Vanderkwaak T.J.; Alvarez R.D.
Dr. R.D. Alvarez, University of Alabama, Department of Obstetrics/Gynecology, Division of Gynecologic Oncology, 618 South 20th Street, Birmingham, AL 35233-7333 United States
AUTHOR EMAIL: rdalvarez@aol.com
Current Opinion in Obstetrics and Gynecology (CURR. OPIN. OBSTET. GYNECOL.) (United Kingdom) 1999, 11/1 (29-34)

CODEN: COOGE ISSN: 1040-872X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 38

Immune based therapies for ovarian carcinoma continue to evolve. The current status of **antibody**, **antibody conjugates**, **cytokine**, cellular, and vaccine based immunotherapy is reviewed. Novel gene transfer strategies that will play an increasing important role in the evolution of immunotherapy are also discussed.

02800043
Utility
ANTIGEN-BINDING FUSION PROTEINS

PATENT NO.: 5,767,260
ISSUED: June 16, 1998 (19980616)
INVENTOR(s): Whitlow, Marc, El Sabrante, CA (California), US (United States of America)
Filpula, David, Piscataway, NJ (New Jersey), US (United States of America)
Shorr, Robert, Edison, NJ (New Jersey), US (United States of America)
ASSIGNEE(s): Enzon Inc , (A U.S. Company or Corporation), Piscataway, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 28483]
APPL. NO.: 8-515,903
FILED: August 16, 1995 (19950816)

This application is a division of application Ser. No. 08-323,445, filed Oct. 13, 1994, (status pending).
FULL TEXT: 1616 lines

ABSTRACT

Compositions of, genetic constructions coding for, and methods for producing single-chain and multivalent immunoeffector antigen-binding fusion proteins are provided by the invention. Antigen-binding fusion proteins having phospholipase A activating protein and/or tumor necrosis factor fragments are also provided by the invention. Genetic sequences coding for single-chain and multivalent immunoeffector antigen-binding fusion proteins are disclosed.

51/7/71 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0225486 DBA Accession No.: 98-07083 PATENT
Vector for expressing **fusion** of toxin and **antibody** or **cytokine** in Escherichia coli - recombinant fusion protein preparation by vector plasmid pCANTAB or plasmid pHEN expression, used for tumor therapy
AUTHOR: Barth S; Engert A; Matthey B; Diehl V
CORPORATE SOURCE: Cologne, Germany.
PATENT ASSIGNEE: Barth S 1998
PATENT NUMBER: EP 841400 PATENT DATE: 980513 WPI ACCESSION NO.: 98-252944 (9823)
PRIORITY APPLIC. NO.: EP 96117908 APPLIC. DATE: 961108
NATIONAL APPLIC. NO.: EP 96117908 APPLIC. DATE: 961108
LANGUAGE: German
ABSTRACT: A new vector for expressing a recombinant fusion protein consisting of a toxin and a ligand specific for particular tumor cells, has DNA sequences: for a region of an antibody and/or cytokine; for the toxin or its catalytically active region; and for segments that allow detection and characterization of the recombinant protein and unique restriction endonuclease cleavage sites. The new vector has a multiple cloning site for insertion of variable antibody regions and is provided with a (Gly4-Ser)3 linker and is directly compatible with plasmid pCANTAB and plasmid pHEN, providing that the unique restriction endonuclease sites in the multiple cloning site are not present in the coding region for the appropriate modified toxin. The new vectors may be used to express fusion proteins in Escherichia coli, which may be used for tumor therapy. The vectors allow direct cloning of single chain Fv genes from commercial phage systems, overcome problems of leakage and allow for targeted exchange of all relevant sequence fragments. (6pp)

toxin, or amino [redacted]r or polysaccharide from a ba[redacted]ium or fungus cell wall), to stimu[redacted]e an immune response to an ant[redacted]n, for therapy of a virus bacterium [redacted]fungus or retro virus infectio[redacted]or in interleukin-2 receptor-bearing tumor imaging. The fusion protein may be produced by culturing a cell line transformed with an encoding gene, and recovering the recombinant product. The fusion protein may also be used as an adjuvant in vaccine or hybridoma generation. (63pp)

51/7/76 (Item 8 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0215590 DBA Accession No.: 97-10711 PATENT
New recombinant **antibody cytokine fusion** proteins - containing immunoglobulin heavy chain and cytokine e.g. tumor necrosis factor-alpha, interleukin-2 or lymphokine, for use in therapy
AUTHOR: Gillies S D
CORPORATE SOURCE: Hingham, MA, USA.
PATENT ASSIGNEE: Gillies S D 1997
PATENT NUMBER: US 5650150 PATENT DATE: 970722 WPI ACCESSION NO.: 97-384621 (9735)
PRIORITY APPLIC. NO.: US 281238 APPLIC. DATE: 940727
NATIONAL APPLIC. NO.: US 281238 APPLIC. DATE: 940727
LANGUAGE: English
ABSTRACT: A new recombinant immunoconjugate contains an immunoglobulin (Ig) heavy chain and a cytokine, preferably a tumor necrosis factor-alpha, interleukin-2 or lymphokine forming a dimeric or multimeric structure, e.g. a lymphotoxin or granulocyte-macrophage colony stimulating factor. The amino acid terminus of the cytokine is linked by a peptide bond to the carboxy-terminus of the Ig chain, and a proteolytic site is located between the Ig heavy chain and the cytokine. The Ig heavy chain contains a mouse N-terminal variable region specific for a cancer cell or a virus-infected cell, and human CH1 and CH2 domains, and optionally a CH3 domain. The immunoconjugate displays both antigen-binding specificity and cytokine activity (eliciting a cytotoxic or proliferative response in cells), and can be used to deliver selectively a cytokine to a target cell in vivo. Localized biological responses e.g. T-lymphocyte stimulation and activation, inflammatory response and antibody-dependent cellular cytotoxicity, can be induced and the immunoconjugates may be useful for treating viral infections or cancer. (17pp)

51/7/87 (Item 19 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0113787 DBA Accession No.: 91-01429 PATENT
Conjugate consisting of antibody and biological response modifier - especially lymphokine or cytokine e.g. tumor necrosis factor, interleukin or interferon, which may be recombinant, conjugated to a monoclonal antibody for targeted drug delivery
PATENT ASSIGNEE: Res.Develop.Found. 1990
PATENT NUMBER: EP 396387 PATENT DATE: 901107 WPI ACCESSION NO.: 90-336799 (9045)
PRIORITY APPLIC. NO.: US 348237 APPLIC. DATE: 890505
NATIONAL APPLIC. NO.: EP 90304734 APPLIC. DATE: 900501
LANGUAGE: English
ABSTRACT: Composition (I) comprises a conjugate of an antibody, especially a monoclonal antibody (MAb), directed toward a tumor-associated antigen, and a biological response modifier (BRF), especially tumor necrosis factor, interleukin-1, interleukin-2, interleukin-3, interleukin-4, interleukin-5, interleukin-6, interleukin-7, lymphotoxin, interferon-alpha, interferon-beta or interferon-lambda. The conjugate is obtained using bifunctional protein coupling agents or as a result of a gene fusion between the gene encoding the BRF and a gene encoding the antigen recognition site of the MAb. The MAb is typically directed toward a breast carcinoma antigen (I5A8 antibody) or a melanoma antigen (ZME-018 antibody). It is obtained by conventional hybridoma construction techniques. The BRF may be obtained by insertion of the desired gene into a vector and transformation of a host, especially Escherichia coli, with the vector to obtain transformants producing proteins that retain the desired activity to be delivered to the targeted sites. The conjugate is used to target the BRF to the site

57/3/2 (Item 2 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01431939 SUPPLIER NUMBER: 14702023 (USE FORMAT 7 OR 9 FOR FULL TEXT)
The bystander effect - tumor regression when a fraction of the tumor mass is genetically modified. (Periodical Report) (Abstract)
Freeman, S.M.; **Abboud, C.N.**; Whartenby, K.A.; Packman, C.H.; Koeplin, D.S.; Moolten, F.L.; Abraham, G.N
Cancer Researcher Weekly, p24(1)
Dec 6,
1993
DOCUMENT TYPE: Abstract PUBLICATION FORMAT: Newsletter LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Academic; Professional
WORD COUNT: 227 LINE COUNT: 00028

57/3/3 (Item 3 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01420482 SUPPLIER NUMBER: 13922603 (USE FORMAT 7 OR 9 FOR FULL TEXT)
An anti-cancer drug delivery approach using gene-modified tumor cells. (Research Report)
Freeman, S.M.; Whartenby, K.A.; **Abboud, C.N.**; Moolten, F.L.; Koeplin, D.S.; Abraham, G.N
Cancer Researcher Weekly, p24(1)
June 7,
1993
PUBLICATION FORMAT: Newsletter LANGUAGE: English RECORD TYPE: Fulltext
TARGET AUDIENCE: Academic; Professional

57/3/14 (Item 10 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

01829702 3615260
Cytokine regulation of early human lymphopoiesis
Ryan, D.H.; Nuccie, B.L.; Ritterman, I.; Liesveld, J.L.; **Abboud, C.N.**
Univ. Rochester, Sch. Med. and Dent., Box 608, 601 Elmwood Ave., Rochester, NY 14642, USA
J. IMMUNOL. vol. 152, no. 11, pp. 5250-5258 (1994)
ISSN: 0022-1767
DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH

51/7/84 (Item 16 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0142764 DBA Accession No.: 93-00816
Adapting antibodies for clinical use - monoclonal antibody engineering technology; a review
AUTHOR: Hawkins R E; Llewelyn M B; Russell S J
CORPORATE SOURCE: Medical Research Council Centre and Addenbrooke's Hospital, Cambridge CB2 2QH, UK.
JOURNAL: Br.Med.J. (305, 6865, 1348-52) 1992
CODEN: BMJOAE
LANGUAGE: English
ABSTRACT: The engineering of monoclonal antibodies (MAbs) for clinical use is reviewed as follows: (1) chemical modification of MAbs by proteolytic cleavage or chemical coupling; (2) genetic modification of MAbs - (a) production of recombinant Fv and Fab **antibody** fragments, (b) production of **fusion** proteins comprising **antibody** and enzyme, toxin or **cytokine** moieties, (c) humanized antibody production by preparation of chemical antibodies and complementarity determining region-grafted antibodies, and (d) production of bispecific antibodies having 2 antigen binding sites, each with a different binding specificity; (3) rapid cloning of antibody genes using the polymerase chain reaction for e.g. V gene amplification; (4) phage display systems; (5) phage antibody libraries; (6) the potential of phage antibody technology for production of human MAbs, phage 'polyclonals' and antiself antibodies, and for affinity maturation on phage; and (7) the future of antibody engineering. (25

51/7/35 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04764983 BIOSIS NO.: 000080068110
MEDIATION OF MACROPHAGE REACTIONS IN IMMUNE TISSUE INJURY

AUTHOR: HONDA M; YOSHIMURA T; MIURA K; HAYASHI H
AUTHOR ADDRESS: DEP. PATHOL., KUMAMOTO UNIV. MED. SCH., 2-2-1 HONJO KUMAMOTO 860, JPN.

JOURNAL: ACTA PATHOL JPN 35 (2). 1985. 269-280.
FULL JOURNAL NAME: Acta Pathologica Japonica
CODEN: APJAA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The chemotactic specificity of 3 types of macrophage chemotactic factors (MCF)-a, MCF-b and MCF-c, from delayed hypersensitivity reaction (DHR) skin sites in guinea pigs, was analyzed. MCF-c shared common antigenicity with the macrophage chemotactic lymphokine released from bovine .gamma. globulin (BGG) and horse radish peroxidase (HRPO)-stimulated lymphocytes, using an immunoadsorbent column **conjugated** with anti-MCF-c **antibody**. These purified **lymphokines** were very similar, or possibly identical in terms of physicochemical and serological properties. BCG-induced lymphokine seemed to exist as complexes with serum protein at the skin site. A change in the proportion of each MCF was observed during the development of DHR. Furthermore, MCF-a and MCF-b attracted Ia- M1 cell line cells, while MCF-c attracted Ia+ cells. Moreover, the responsive guinea-pig monocytes were divided mainly into 2 distinctive migrating subpopulations. One subpopulation was responsive to MCF-a and MCF-b and the majority of responding cells were Ia-. The 2nd subpopulation was responsive to MCF-c and the predominant cell type was Ia-. The data suggest that macrophage reactions in the DHR are mediated by MCF-a, MCF-b and MCF-c and that MCF-c attracts Ia bearing accessory macrophages and MCF-a and MCF-b attract Ia- macrophages.

51/7/36 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04202781 BIOSIS NO.: 000077028825
MONOCYTE CHEMO TAXIS MEDIATED BY FORMYLMETHIONYLLEUCYLPHENYL ALANINE CONJUGATED WITH MONO CLONAL ANTIBODIES AGAINST HUMAN OVARIAN CARCINOMA

AUTHOR: OBRIST R; REILLY R; LEAVITT T; KNAPP R C; BAST R C JR
AUTHOR ADDRESS: SIDNEY FARBER CANCER INST., 44 BINNEY ST., BOSTON, MA 02115, U.S.A.

JOURNAL: INT J IMMUNOPHARMACOL 5 (4). 1983. 307-314.
FULL JOURNAL NAME: International Journal of Immunopharmacology
CODEN: IJIMD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Availability of a chemically defined chemoattractant (fMLP

51/7/25 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10339625 BIOSIS NO.: 199698794543
Involvement of B lymphocytes in the growth inhibition of human pulmonary melanoma metastases in athymic nu/nu mice by an antibody-lymphotoxin fusion protein.

AUTHOR: Reisfeld Ralph A(a); Gillies Stephen D; Mendelsohn John; Varki Nissi M; Becker Juergen C
AUTHOR ADDRESS: (a)Dep. Immunol., Scripps Res. Inst., 10666 N. Torrey Pines Rd., La Jolla, CA 92037, USA

JOURNAL: Cancer Research 56 (8):p1707-1712 1996
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Antibody-cytokine fusion** proteins can target biologically active **cytokines** to various tumor sites, achieving local concentrations sufficient to induce host immune responses leading to tumor elimination. Here, we demonstrate the therapeutic efficacy of a tumor-specific antibody-lymphotoxin fusion protein (ch225-LT) on xenografted pulmonary metastases of human melanoma. In vitro studies indicated a direct cytotoxic effect of such constructs on melanoma cells via the induction of apoptosis, as demonstrated by cell cycle analysis and DNA fragmentation. However, ch225-LT lacked any therapeutic effect in immune deficient C.B17 scid/ beige and scid/scid mice, indicating the insufficiency of this direct mechanism in vivo. In contrast, in athymic nu/nu mice, ch225-LT completely inhibited outgrowth of the xenografted tumor. This therapeutic effect was accompanied by infiltrations of CD45+, Mac-1+, and asialo-GM1+ cells into the tumor; B220+ cells were present in the surrounding tissue and the periphery of the tumor. The functional role of asialo-GM1+ cells was confirmed by in vivo depletion studies. Our data indicate that an antibody-lymphotoxin fusion protein effectively inhibits the growth of disseminated melanoma metastases by mechanisms that function in the absence of mature T cells, but require B, NK, and other asialo-GM1+ cells.

51/7/19 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11104651 BIOSIS NO.: 199799725796
Characterization of **chemokine-antibody fusion** proteins for cancer immunotherapy.

AUTHOR: Challita Pia-Maria; Abboud Camille N; Rosell Karen E; Rosenblatt Joseph D

JOURNAL: Experimental Hematology (Charlottesville) 25 (8):p889 1997

CONFERENCE/MEETING: 26th Annual Meeting of the International Society for Experimental Hematology Cannes, France August 24-28, 1997
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English

51/7/17 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11252211 BIOSIS NO.: 199800033543
Immunocytokines: A new approach to immunotherapy of melanoma.

AUTHOR: Reisfeld Ralph A(a); Becker Juergen C; Gillies Stephen D
AUTHOR ADDRESS: (a)Scripps Res. Inst., IMM13, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA

JOURNAL: Melanoma Research 7 (SUPPL. 2):pS99-S106 Aug., 1997
ISSN: 0960-8931
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Targeted interleukin-2 (IL-2) therapy with immunocytokines (i.e. **antibody-cytokine fusion** proteins) is effective in eradicating established hepatic and pulmonary metastases of melanoma in animal model systems.The effector mechanisms responsible for this antitumor effect in syngeneic, immunocompetent mice involves mainly CD8+T cells. This was clearly indicated by immunohistochemical analyses, in vivo depletion studies and cytotoxicity tests. Such CD8+T cells, isolated from tumor-bearing mice after immunocytokine therapy, exerted a major histocompatibility complex class I-restricted cytotoxicity against the same tumor in vitro. Because of this cellular immune response, antibody-directed IL-2 therapy can even address established metastases displaying extensive heterogeneity in the expression of the targeted antigen. The effector mechanisms induced by immunocytokines facilitate partial regressions of large subcutaneous melanoma exceeding more than 5% of the body weight. These results demonstrate the ability of immunocytokines to induce a T-cell-dependent host immune response capable of eradicating established melanoma metastases in clinically relevant organs and offers an effective, new tool for immunotherapy of malignant melanoma.

51/7/11 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11862686 BIOSIS NO.: 199900108795
Characterization of a **RANTES** anti-HER2/neu **antibody fusion** protein for cancer immunotherapy.

AUTHOR: Challita-Eid Pia M(a); Abboud Camille N; Morrison Sherie L; Hilchey Shannon P; Penichet Manuel L; Rosebrough Scott F; Rosenblatt Joseph D
AUTHOR ADDRESS: (a)Dep. Mircobiol. Mol. Genet., Mol. Biol. Inst., UCLA, Los Angeles, CA, USA

JOURNAL: Blood 92 (10 SUPPL. 1 PART 1-2):p24A Nov. 15, 1998

CONFERENCE/MEETING: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998
SPONSOR: The American Society of Heamatology

ISSN: 0006-4971
RECORD TYPE: Citation

06175824 EMBASE No: 1995198924

The RANTES chemokine. A new target for immunomodulatory therapy?

Pattison J.M.; Nelson P.J.; Krensky A.M.
Department of Pediatrics, Stanford University Medical Center,Stanford, CA 94305-5119 United States

Clinical Immunotherapeutics (CLIN. IMMUNOTHER.) (New Zealand) 1995, 4/1 (1-8)

CODEN: CIMME ISSN: 1172-7039
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

RANTES is a member of the C-C family of chemoattractant cytokines (chemokines). It is secreted by T lymphocytes late after activation, and by fibroblasts, epithelial cells and endothelial cells after stimulation with tumour necrosis factor-alpha, interleukin-1beta and interferon-gamma. RANTES is a potent chemoattractant for monocytes, memory T cells, basophils and eosinophils. It also triggers basophil degranulation and activates eosinophils. RANTES is highly expressed in acute cell-mediated transplant rejection, in chronic inflammatory diseases such as sarcoidosis and atherosclerosis, and by some malignancies. This novel cytokine may play a pivotal role in the recruitment of the mononuclear cell infiltrate present in these conditions, and represents a potential target for new therapeutic

In mice, chemokines, su[redacted]s IP-10, **RANTES**, and TCA3, hav[redacted]resulted in **tumor** regression a[redacted]munity to subsequent tumor c[redacted]ge. Those chemokines that are a[redacted]ostatic (e.g., PF4, IP-10, and [redacted]G) can also induce tumor regression by reducing the tumor blood supply. Conversely, IL-8, which is angiogenic, can promote tumor growth. Our studies show that nasopharyngeal cell line cells (FADU) show a chemotactic as well as a proliferative response to MCP-1. In addition, a variant murine T cell lymphoma cell line Esb-MP, unlike the parental variant Esb, was selectively chemoattracted by murine MCP-I/JE. When injected s.c. into mice, the Esb-MP variant metastasized to the kidney with much higher frequency than the Esb variant. Both cultured kidneys from normal mice and a mesangial cell line constitutively produced chemoattractants that acted on Esb-MP but not Esb parental cells. Purification to homogeneity of these chemoattractants led to the identification of RANTES and JE. These results demonstrate that some chemokines may promote tumor growth and organ-specific metastatic spread of those tumors that have adapted and become responsive to chemokines. Finally, tumors appear to use numerous adaptive mechanisms to subvert and suppress the immune system. More effective therapy with cytokines and chemokines will require better characterization of the means by which tumors develop resistance to cytokines and overcome the immune system. Only then can we develop appropriate therapeutic approaches to antagonize cancer-induced immunosuppression.

48/7/45 (Item 27 from file: 73)
DIALOG(R)File 73:EMBASE

06615236 EMBASE No: 1996280013
RANTES secretion by gene-modified **tumor** cells results in loss of tumorigenicity in vivo. Role of immune cell subpopulations
Mule J.J.; Custer M.; Averbook B.; Yang J.C.; Weber J.S.; Goeddel D.V.; Rosenberg S.A.; Schall T.J.
Department of Surgery, MSRB-1, University of Michigan, 1150 W. Medical Center Dr.,Ann Arbor, MI 48103-0666 United States
Human Gene Therapy (HUM. GENE THER.) (United States) 1996, 7/13 (1545-1553)

CODEN: HGTHE ISSN: 1043-0342
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

An immunogenic murine fibrosarcoma cell line was genetically modified to express and produce the human RANTES chemokine stably. In in vitro chemotaxis assays purified recombinant human RANTES as well as human **RANTES** secreted by the modified murine **tumor** cells were strongly chemoattractant for mouse CD8sup +/Thy-1sup + **tumor** -infiltrating lymphocytes (TIL). **RANTES** production did not alter the growth of these cytokine gene-modified tumor cells in vitro, but injection of RANTES-secreting cells resulted in the abolition of the ability of those cells to form solid tumors in vivo. The growth of tumors could be restored by co-administration of monoclonal antibodies that inhibit the function of various subsets of immune cells. For example, depletion of CD8sup + T cells by antibody administration resulted in complete restoration of solid **tumor** formation by **RANTES**-secreting cells, whereas depletion of the CD4sup + T cell population resulted in a partial restoration of tumor formation. Additionally, administration of an anti-CR3 monoclonal antibody known to inhibit the in vivo migration of macrophages also completely restored the **tumorigenicity** of **RANTES**-secreting fibrosarcoma cells. Thus, the human **RANTES** chemokine can abolish **tumorigenicity** of an immunogenic fibrosarcoma in an in vivo murine model, and this process is mediated by various subpopulations of immune effector cells.

48/6/107 (Item 4 from file: 76)
01974553 3824552
Subcellular mechanisms of eosinophil degranulation: The role of **RANTES**, interleukin-5 and **tumor** necrosis factor- alpha
INT. ARCH. ALLERGY IMMUNOL.
? t s48/7/1,20,45,55

48/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11279367 BIOSIS NO.: 199800060699
Characterization of a **RANTES**-antibody fusion protein for **cancer** immunotherapy.

AUTHOR: Challita P M; Abboud C N; Rosell K E; Penichet M; Morrison S L; Rosenblatt J D
AUTHOR ADDRESS: Dep. Microbiol. Mol. Genetics, Mol. Biol. Inst., UCLA, Los Angeles, CA, USA

JOURNAL: Blood 90 (10 SUPPL. 1 PART 2):p40B Nov. 15, 1997

CONFERENCE/MEETING: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology

ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

48/7/20 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07199159 EMBASE No: 1998096138
Prospects for cytokine and chemokine biotherapy
Oppenheim J.J.; Murphy W.J.; Chertov O.; Schirrmacher V.; Ji Ming Wang
J.J. Oppenheim, Lab. of Molecular Immunoregulation, Building 560, National Cancer Institute, Frederick, MD 21702-1201 United States
Clinical Cancer Research (CLIN. CANC. RES.) (United States) 1997, 3/12 II (2682-2686)

CODEN: CCREF ISSN: 1078-0432
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 36

Cytokines with immunostimulating effects have the capacity to induce tumor immunity in animal models, whereas some cytokines interfere with tumor growth based on their angiostatic effects. Despite these capabilities, cytokines, such as IFN-alpha, IFN-gamma, tumor necrosis factor, interleukin (IL)- 1, and IL-2, have had limited clinical efficacy and many undesirable side effects. In preclinical models, cytokines can even promote tumor growth and increase metastatic spread. Although chemokines have had limited clinical evaluation, studies of animal models show that they can also have tumor- suppressive or tumor-enhancing effects.

20/3/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11869165 BIOSIS NO.: 199900115274
Lymphoblastic leukemia cells express CXCR-4 and migrate through endothelium in response to SDF-1: Implications for leukemia cell vaccination.

AUTHOR: Cardoso Angelo A; Veiga J Pedro; Ghia Paolo; Afonso Hernani M; Nadler Lee M
AUTHOR ADDRESS: Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA, USA

JOURNAL: Blood 92 (10 SUPPL. 1 PART 1-2):p618A Nov. 15, 1998

CONFERENCE/MEETING: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998
SPONSOR: The American Society of Heamatology

ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

20/3/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11853003 BIOSIS NO.: 199900099112
SDF-1 and its receptor CXCR4 are required for migration of human B cell precursors under stroma and their proliferation in culture.

AUTHOR: Scheidweiler Karl(a); Ritterman Ion; Tang Jihong; Fedyk Eric; Springer Timothy; Ryan Daniel
AUTHOR ADDRESS: (a)Univ. Rochester, Rochester, NY, USA

JOURNAL: Blood 92 (10 SUPPL. 1 PART 1-2):p24A Nov. 15, 1998

CONFERENCE/MEETING: 40th Annual Meeting of the American Society of Hematology Miami Beach, Florida, USA December 4-8, 1998
SPONSOR: The American Society of Heamatology

ISSN: 0006-4971
RECORD TYPE: Citation

24/7/65 (Item 8 from file: 159)
DIALOG(R)File 159:Cancerlit

01349492 97282201 MEDL/97282201
Fractalkine--a strange attractor in the chemokine landscape.
Schall T
DNAX Research Institute, Palo Alto, CA 94304, USA. schall@dnax.org
Immunol Today; 18(4):147 1997 ISSN 0167-5699 Journal Code: AEA
Languages: ENGLISH

27/7/2 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06646294 EMBASE No: 1996311152
Combined chemokine and cytokine gene transfer enhances antitumor immunity
Dilloo D.; Bacon K.; Holden W.; Zhong W.; Burdach S.; Zlotnik A.; Brenner M.
Division Bone Marrow Transplantation, St. Jude Children's Research Hosp., 332 North Lauderdale,Memphis, TN 38105 United States
Nature Medicine (NAT. MED.) (United States) 1996, 2/10 (1090-1095)

CODEN: NAMEF ISSN: 1078-8956
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The probability of producing a specific antitumor response should be increased by multiplying the number of T lymphocytes that encounter the malignant cells. We tested this prediction in a murine model, using a recently discovered T-cell chemokine, **lymphotactin** (Lptn). This chemokine increased **tumor** cell infiltration with CD4sup + lymphocytes but generated little antitumor activity. Coexpression of the T-cell growth factor interleukin-2 however, greatly expanded the T lymphocytes attracted by Lptn, affording protection from the growth of established tumor in a CD4sup + and CD8sup + T cell-dependent manner. Lesser synergy was seen with GM-CSF. Hence coexpression of a T-cell chemokine and T-cell growth factor potentiates antitumor responses in vivo, suggesting a general strategy to

33/7/4 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11322453 BIOSIS NO.: 199800103785
Anti-**tumor** functions of IP-10 and **Mig**.

AUTHOR: Tannenbaum C S; Tubbs R; Armstrong D; Finke J; Bukowski R; Hamilton T
AUTHOR ADDRESS: Lerner Res. Inst., Dep. Immunol., Cleveland Clinic Foundation, Cleveland, OH, USA

JOURNAL: Journal of Leukocyte Biology (SUPPL.):p18 1997

CONFERENCE/MEETING: Meeting on Cytokine and Chemokine Signaling in Leukocyte Development and Function held at the Thirty-second National Meeting of the Society for Leukocyte Biology Baltimore, Maryland, USA December 4-7, 1997
SPONSOR: Society for Leukocyte Biology

ISSN: 0741-5400
RECORD TYPE: Citation
LANGUAGE: English

33/7/5 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10899471 BIOSIS NO.: 199799520616
Mig, the monokine induced by interferon-gamma, promotes tumor necrosis in vivo.

AUTHOR: Sgadari Cecilia; Farber Joshua M; Angiolillo Anne L; Liao Fang; Teruya-Feldstein Julie; Burd Parris R; Yao Lei; Gupta Ghanshyam; Kanegane Chiharu; Tosato Giovanna(a)
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JOURNAL: Blood 89 (8):p2635-2643 1997
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mig, the monokine induced by interferon-y, is a CXC chemokine active as a chemoattractant for activated T cells. Mig is related functionally to interferon-inducible protein 10 (IP10), with which it shares a receptor, CXCR3. Previously, IP10 was found to have antitumor activity in vivo. In the present study, murine Mig RNA was found to be expressed at higher levels in regressing Burkitt's lymphoma tumors established in nude mice compared with progressively growing tumors. Daily inoculations of purified recombinant human **Mig** into Burkitt's **tumors** growing subcutaneously in nude mice consistently caused tumor necrosis associated with extensive vascular damage. These effects were indistinguishable from those produced by intratumor inoculations of Burkitt's tumors with IP-10. These results support the notion that Mig, like IP-10, has antitumor activity in vivo. This is a US government work.

33/7/10 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07199159 EMBASE No: 1998096138
Prospects for cytokine and chemokine biotherapy
Oppenheim J.J.; Murphy W.J.; Chertov O.; Schirrmacher V.; Ji Ming Wang
J.J. Oppenheim, Lab. of Molecular Immunoregulation, Building 560, National Cancer Institute, Frederick, MD 21702-1201 United States
Clinical Cancer Research (CLIN. CANC. RES.) (United States) 1997, 3/12 II (2682-2686)

CODEN: CCREF ISSN: 1078-0432
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 36

Cytokines with immunostimulating effects have the capacity to induce tumor immunity in animal models, whereas some cytokines interfere with tumor growth based on their angiostatic effects. Despite these capabilities, cytokines, such as IFN-alpha, IFN-gamma, tumor necrosis factor, interleukin (IL)- 1, and IL-2, have had limited clinical efficacy and many undesirable side effects. In preclinical models, cytokines can even promote tumor growth and increase metastatic spread. Although chemokines have had limited clinical evaluation, studies of animal models show that they can also have tumor- suppressive or tumor-enhancing effects. In mice, chemokines, such as IP-10, RANTES, and TCA3, have resulted in tumor regression and immunity to subsequent tumor challenge. Those chemokines that are angiostatic (e.g., PF4, IP-10, and **MIG**) can also induce **tumor** regression by reducing the tumor blood supply. Conversely, IL-8, which is angiogenic, can promote tumor growth. Our studies show that nasopharyngeal cell line cells (FADU) show a chemotactic as well as a proliferative response to MCP-1. In addition, a variant murine T cell lymphoma cell line Esb-MP, unlike the parental variant Esb, was selectively chemoattracted by murine MCP-I/JE. When injected s.c. into mice, the Esb-MP variant metastasized to the kidney with much higher frequency than the Esb variant. Both cultured kidneys from normal mice and a mesangial cell line constitutively produced chemoattractants that acted on Esb-MP but not Esb parental cells. Purification to homogeneity of these chemoattractants led to the identification of RANTES and JE. These results demonstrate that some chemokines may promote tumor growth and organ-specific metastatic spread of those tumors that have adapted and become responsive to chemokines. Finally, tumors appear to use numerous adaptive mechanisms to subvert and suppress the immune system. More effective therapy with cytokines and chemokines will require better characterization of the means by which tumors develop resistance to cytokines and overcome the immune system. Only then can we develop appropriate therapeutic approaches to antagonize cancer-induced immunosuppression.

36/7/4 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10155028 BIOSIS NO.: 199698609946
Human **MCAF** gene transfer enhances the **metastatic** capacity of a mouse cachectic adenocarcinoma cell line in vivo.

AUTHOR: Nakashima Emi(a); Mukaida Naofumi; Kubota Yuri; Kuno Kouji; Yasumoto Kazuo; Ichimura Fujio; Nakanishi Isao; Miyasaka Masayuki; Matsushima Kouji
AUTHOR ADDRESS: (a)Hospital Pharmacy, Kanazawa Univ., 13-1 Takara-machi, Kanazawa 920, Japan

JOURNAL: Pharmaceutical Research (New York) 12 (11):p1598-1604 1995
ISSN: 0724-8741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: To evaluate the effect of monocyte chemotactic and activating factor (**MCAF**/MCP-I/JE) on **tumor** progression and metastasis. Methods: Cachexia-inducing adenocarcinoma cells (cell line colon 26, clone 20) were transfected with either a control plasmid or **MCAF** expression vector. Spontaneous lung **metastases** were determined in mouse. Results: The production of MCAF reached 0.4 ng/ml in vitro when transfectant cells were cultured at a cell density of 5 times 10-4 cells/ml for 3 days. Transfection of MCAF expression vector did not affect the growth rate in vitro. Also, after **MCAF**-transfection, the size of **tumors** after intra-footpad inoculation was similar to that of the parental cells. When the primary tumors were resected on the 10th day after inoculation, the incidence of spontaneous lung metastasis was less than 20% in both cells. The number of endothelial cells in the primary tumor rapidly increased from the 10th to the 14th day after inoculation, as revealed by immunohistochemical staining. In accordance with enhanced angiogenesis, the incidence rates of spontaneous metastasis increased when the primary tumors were resected on the 14th day after inoculation. Moreover, the spontaneous lung metastases were augmented in the animals injected with MCAF-transfectants compared to those injected with parental cells with a concomitant increase of angiogenesis. Conclusions: These results suggest that **MCAF** may augment the **metastatic** potential by modulating tumor associated angiogenesis.

9/7/13 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

01560462 2683222
Antibody-targeted interleukin 2 stimulates T-cell killing of autologous tumor cells.
Gillies, S.D.; Reilly, E.B.; Lo, Kin Ming; Reisfeld, R.A.
Res. Dep., Abbott Biotech, Inc., 119 Fourth Ave., Needham Heights, MA 02194, USA
PROC. NATL. ACAD. SCI. USA. vol. 89, no. 4, pp. 1428-1432 (1992.)
DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH
SUBFILE: Immunology Abstracts

A genetically engineered fusion protein consisting of a chimeric anti-ganglioside GD2 antibody (ch14.18) and interleukin 2 (IL2) was tested for its ability to enhance the killing of autologous GD2-expressing melanoma target cells by a tumor-infiltrating lymphocyte line (660 TIL). The fusion of IL2 to the carboxyl terminus of the immunoglobulin heavy chain did not reduce IL2 activity as measured in a standard proliferation assay using either mouse or human T-cell lines. Antigen-binding activity was greater than that of the native **chimeric antibody**. Such **antibody-cytokine** fusion proteins may prove useful in targeting the biological effect of IL2 and other cytokines to tumor cells and in this

18/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10990462 BIOSIS NO.: 199799611607
A dendritic-cell-derived C-C chemokine that preferentially attracts naive T cells.

AUTHOR: Adema Gosse J(a); Hartgers Franca; Verstraten Riet; De Vries Edwin; Marland Gill; Menon Satish; Foster Jessica; Xu Yuming; Nooyen Pete; McClanahan Terrill; Bacon Kevin B; Figdor Carl G
AUTHOR ADDRESS: (a)Dep. Tumour Immunol., Univ. Hosp. Nijmegen St. Radboud, Philips van Leydenlaan 25, 6525 EX Nijme, Netherlands

JOURNAL: Nature (London) 387 (6634):p713-717 1997
ISSN: 0028-0836
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Dendritic cells form a system of highly efficient antigen-presenting cells. After capturing antigen in the periphery, they migrate to lymphoid organs where they present the antigen to T cells. Their seemingly unique ability to interact with and sensitize naive T cells gives dendritic cells a central role in the initiation of immune responses and allows them to be used in therapeutic strategies against cancer, viral infection and other diseases. How they interact preferentially with naive rather than activated T lymphocytes is still poorly understood. Chemokines direct the transport of white blood cells in immune surveillance. Here we report the identification and characterization of a C-C chemokine (DC-CK1) that is specifically expressed by human dendritic cells at high levels. Tissue distribution analysis demonstrates that dendritic cells present in germinal centres and T-cell areas of secondary lymphoid organs express this chemokine. We show that DC-CK1, in contrast to RANTES, MIP-1-alpha and interleukin-8, preferentially attracts naive T cells (CD45RA+). The specific expression of DC-CK1 by dendritic cells at the site of initiation of an immune response, combined with its chemotactic activity for naive T cells, suggests that DC-CK1 has an important rule in the induction of immune

3/7/4 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0193758 DBA Accession No.: 96-05165
Specificity of human T-lymphocytes is genetically redirected by chimeric T-body receptors - carcinoembryonic antigen and **Her2/neu** specific **antibody** combining site, transduction element recombinant **chimeric** receptor expression in T-lymphocyte; tumor immunotherapy (conference abstract)
AUTHOR: Kruger M; Bhullar A; Chiang G; Goodenow R; Gregory H; Harney P ; Kahrs A; Killion C; Krapf I; Lundak C; McLaughlin-Taylor E; Reuter J; Rodriquez E; Sulya G; Vernachio J; Williams A
CORPORATE AFFILIATE: Baxter-Healthcare
CORPORATE SOURCE: Gene Therapy Unit, Biotech Group, Baxter Healthcare Corporation, Santa Ana, CA 92705, USA.
JOURNAL: J.Cell.Biochem. (Suppl.21A, 424) 1995
ISSN: 0730-2312 CODEN: JCEBD5
CONFERENCE PROCEEDINGS: Keystone Symposium, 24th Annual Meeting, Gene Therapy and Molecular Medicine, Steamboat Springs, CO, March 26-April 1, 1995.
LANGUAGE: English
ABSTRACT: A T-body is a genetically modified chimeric receptor comprising the combining site specificity of an antibody with a defined signal transduction element which may be used for cancer immunotherapy. Introduction of T-bodies into T-lymphocytes (T-cells) allows generation of T-cells with antibody specificity independent of major histocompatibility complex restriction, while maintaining T-cell effector function. Chimeric genes were constructed using the antigen binding domains of monoclonal antibodies specific for carcinoembryonic antigen or Her2/neu (tumor-associated antigens of colon and mamma carcinoma, respectively). Single chain antibody variable regions (VL/VH) were linked to different signal transducing subunits (TCR-beta, CD3-zeta, FcRIII-gamma) and cloned into retro virus vectors. The vectors introduced T-body genes into human peripheral blood T-cells, tumor infiltrating lymphocytes, T-cell lines and other cell types. The T-bodies were expressed on the cell surface and mediated T-cell cytokine secretion. Transduction efficiency in human peripheral blood

51/7/79 (Item 11 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0193665 DBA Accession No.: 96-05072 PATENT
Hybrid molecules comprising G-CSF linked to a monoclonal antibody, fragment or ligand which recognizes a specific antigen - human recombinant granulocyte colony stimulating factor-monoclonal antibody Fab' or F(ab)2 fragment fusion protein preparation for use as an antitumor agent
AUTHOR: Mele A; Rotondaro L; Di Loreto M; D'Alatri L
CORPORATE SOURCE: Pomezia, Italy.
PATENT ASSIGNEE: Menarini 1996
PATENT NUMBER: WO 9604305 PATENT DATE: 960215 WPI ACCESSION NO.: 96-129334 (9613)
PRIORITY APPLIC. NO.: IT 94MI1694 APPLIC. DATE: 940804
NATIONAL APPLIC. NO.: WO 95EP3060 APPLIC. DATE: 950801
LANGUAGE: English
ABSTRACT: Hybrid molecules useful in antitumor treatment are claimed, which consist of granulocyte colony stimulating factor (G-CSF) linked to a monoclonal antibody, a fragment thereof, or a ligand which recognizes a specific antigen. The G-CSF is preferably human recombinant G-CSF, and is chemically linked to the antibody or ligand. The antibody is specific for a cell surface receptor, preferably epidermal growth factor receptor, especially that produced by cell line DSM ACC2150. The antibody fragments are Fab' or F(ab)2 fragments of this antibody and the hybrid molecule is produced by chemical linkage or recombinant DNA techniques. The molecules stimulate an immune response in vivo against human tumor cells expressing the target antigen which is stronger than that obtained with a mixture of the antibody or ligand and G-CSF. The hybrid molecules consist of antibody fragment having a smaller molecular size and are advantageous as they have favorable pharmokinetics, reduced immunogenicity and an increased capacity to penetrate tissues and reach solid tumor mass. (21pp)

51/7/74 (Item 6 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0220461 DBA Accession No.: 98-02058 PATENT
Antagonist of human interleukin-1-gamma - human recombinant interleukin-1-gamma and **antibody**, Fc fragment, **cytokine** or **chemokine fusion** protein expression, for use as an immunomodulator, antiallergic, diagnostic, etc.
AUTHOR: Sana T R; Timans J C; Hardiman G T; Kastelein R A; Bazan J F
CORPORATE SOURCE: Kenilworth, NJ, USA.
PATENT ASSIGNEE: Schering-USA 1997
PATENT NUMBER: WO 9744468 PATENT DATE: 971127 WPI ACCESSION NO.: 98-018522 (9802)
PRIORITY APPLIC. NO.: US 651998 APPLIC. DATE: 960520
NATIONAL APPLIC. NO.: WO 97US7282 APPLIC. DATE: 970516
LANGUAGE: English
ABSTRACT: A new human interleukin-1-gamma (IL-1g)-antagonist, e.g. an antibody or binding fragment, or a human IL-1g receptor, may be used in therapy of an IL-1g-related condition. A fusion protein or conjugate containing human IL-1g and PEG or an Ig chain, Fc fragment, another cytokine or a chemokine, may be used as a human IL-1g-agonist. DNA encoding the fusion protein may be inserted in a vector for recombinant expression in a host cell. An anti-idiotype antibody with human IL-1g-agonist or -antagonist activity is also new. The product is useful in therapy of immune disorders, allergy or infectious disease. The antibody and recombinant protein may be used in diagnostic assays. In an example, inbred BALB/c mice were immunized i.p. with human recombinant IL-1g, and hybridomas were produced from spleen cells, for monoclonal antibody production. (63pp)

51/7/75 (Item 7 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0216515 DBA Accession No.: 97-11636 PATENT
New **antibody-cytokine fusion** proteins - monoclonal **antibody** and e.g. **lymphokine fusion** protein, for use as an immunostimulant, adjuvant or in cancer diagnosis
AUTHOR: Harvill E T; Morrison S L
CORPORATE SOURCE: Los Angeles, CA, USA.
PATENT ASSIGNEE: Harvill E T; Morrison S L 1997
PATENT NUMBER: WO 9730089 PATENT DATE: 970821 WPI ACCESSION NO.: 97-424981 (9739)
PRIORITY APPLIC. NO.: US 11569 APPLIC. DATE: 960213
NATIONAL APPLIC. NO.: WO 97US1420 APPLIC. DATE: 970211
LANGUAGE: English
ABSTRACT: A new **antibody-cytokine fusion** protein has the formula (Ab)-L-(Ck), where Ab is an antibody (preferably an anti-dansyl monoclonal antibody, MAb), L is a covalent bond or linker (1-10 or preferably 1-5 amino acids, e.g. Cys), and Ck is a cytokine, lymphokine or fragment (e.g. interleukin, macrophage arming factor, lymphocyte inhibition factor, monocyte chemotactic and activating factor or granulocyte-macrophage colony stimulating factor). The fusion protein may be used in a composition with a dansylated antigen (e.g. a retro virus coat protein, other virus coat protein, enterotoxin, other bacterium toxin, fungus protein, antigenic region of a protein or